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SAN FRANCISCO, CALIFORNIA 94143

A Letter

August 5, 1993

Dr. H. McAllister
Research Director
Council for Tobacco Research USA
4th Floor
900 3rd Avenue
New York, New York 10022
Tel #: (212) 421-8885

Dear Dr. McAlliste;

I am writing to request an application form to apply for a grant from The Council for Tobacco Research USA. The proposal, will be entitled "Neuroendocrine Mechanisms of Nicotinic Effects on the Inflammatory Process". The studies we propose would be based on our previous studies of neurogenic mechanisms of inflammation and our preliminary work on the role of neuroendocrine mechanisms in the inflammatory process. We have developed the hypothesis that the inflammatory process is a physiological tissue reparative and protective mechanism that, under unusual circumstances, contributes to pathological changes in the body (inflammatory diseases). Our previous studies have provided extensive evidence for a contribution of the sympathetic nervous system (including the sympathetic-adrenal medullary axis) and the hypothalamic- pituitary-adrenal cortical axis to the inflammatory process. Because of its potent effects on both of these systems, we have begun to investigate the actions of nicotine on the inflammatory process. The proposed studies will investigate the effects of nicotine on aspects of neurogenic inflammation including plasma extravasation, neutrophil attraction, tissue damage and wound healing, in the skin, synovial joint and gastrointestinal tract. Because nicotine is an agonist of nicotinic acetylcholine receptors, these studies will also yield information about the relationship beteen endogenous acetylcholine neural pathways and inflammatory mechanisms.

Since previous clinical evidence suggests that nicotine may have beneficial effects in some inflammatory diseases (e.g., inflammatory bowel disease) while adversely affecting others (e.g., rheumatoid arthritis), we will also evaluate the effects of nicotine on neurogenic inflammation in animal models of these diseases. In addition to elucidating the mechanisms of adverse effects of nicotine, these studies may reveal beneficial effects of nicotine in alleviating inflammatory disease. We can speculate that in the future such beneficial effects might be realized clinically in the form of nicotine-based therapies for the treatment of inflammatory diseases. In this regard, it is interesting to note that tachyphylaxis does not occur for some of the inflammation-related effects of nicotine.

We estimate the the budget for grant proposal will be approximately $90,000.

Sincerely,

Jon D. Levine, M.D., Ph.D.
Professor of Medicine, Neuroscience,
Anatomy, and Oral Surgery
Director, NIH Pain Center (UCSF)